Renal Disease Secondary to Metabolic Disorders or Physiological Deficiency States

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■ *Significant alterations in the structure and functions of the kidney are caused by a number of metabolic disturbances and deficiencies of physiological substances. These include intercapillary glomerulosclerosis, gout, hypercalcemia, hereditary cystinuria, potassium depletion, pyrophosphates deficiency, vitamin D deficiency and liver disorders. Some of these metabolic disorders are secondary to drug ingestion.*

SIGNIFICANT ALTERATIONS in the structure and function of the kidney are caused by a number of metabolic disturbances and deficiencies of physiological substances. In some of these conditions, the cause of renal derangement can be directly related to the metabolic disorder or deficiency state; in others, the association is significant statistically, but the causal relationship is less apparent. The most frequent and striking example of the latter is intercapillary glomerulosclerosis or Kimmelstiel-Wilson syndrome, associated with diabetes mellitus.

The intercapillary glomerulosclerosis of diabetes mellitus has at least two possible causes: (1) It may be a complication of the prolonged absolute or relative insulin deficiency and the resultant metabolic abnormalities, or (2) it may be due to an inherited susceptibility, operating concurrently with the metabolic defect, and progressing without regard to the degree of control of metabolic abnormalities. Unfortunately, diabetic glomerulosclerosis is rarely persistent alone; renal disease associated with diabetes mellitus usually consists of glomerulosclerosis, severe hyaline arteriolosclerosis and focal or diffuse pyelonephritis. The clinical manifestations usually are determined by the predominant lesion. There is suggestive evidence that careful control of diabetes can minimize or postpone the development of clinically important renal disease.[1]

Although nephropathy associated with diabetes can be suspected from certain laboratory evaluations (creatinine clearance, phenolsulfonphthalein excretion, urinary sediment examination, quantitative protein excretion and quantitative urine culture), a definitive diagnosis depends upon the results of histological examination of kidney tissue, usually obtained by needle biopsy. Intercapillary glomerulosclerosis is rarely the cause of the renal dysfunction in patients who do not have diabetic retinopathy (capillary microaneurysms).

There is no specific treatment for diabetic intercapillary glomerulosclerosis or the accompanying arteriolosclerosis. Treatment of urinary tract infection may be specific, but all other sequelae of renal dysfunction, which do not differ from those of other forms of renal failure with or without the nephrotic syndrome, must be treated symptomatically.

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Although we doubt that there is anything characteristic about the type of diabetes mellitus associated with diabetic nephropathy, we believe that good control of the diabetes may decrease the renal morbidity.

The renal lesion associated with the *gouty trait* (hereditary or familial hyperuricemia) also is associated with three changes: Urate deposition in the medulla, severe arteriolosclerosis and focal or diffuse pyelonephritis. Evidence of renal disease is present in approximately 20 per cent of adults who have chronic hyperuricemia, regardless of whether overt attacks of gouty arthritis have occurred. In fact, severe renal failure may be seen in the complete absence of arthritis. The renal lesion appears to be more related to hyperuricemia than to excess excretion of uric acid. Most patients with the gouty trait do not have hyperuricosuria. The deposition of urate crystals in the medulla of the kidney is followed by fibrosis and tubular distortion, which predisposes the "gouty kidney" to urinary tract infection. Urate stones may or may not accompany the renal lesions.

Diagnosis of the gouty trait requires repeated demonstration of hyperuricemia when the patient is not taking drugs that lower the renal clearance of uric acid (for example, thiazides or aspirin). Percutaneous renal biopsy is seldom helpful in making a diagnosis of gouty nephropathy because the urate deposits in the medulla are rarely seen in the usual specimen. Treatment is aimed at reducing the uric acid level of the blood, which is accomplished by giving drugs (probenecid, sulfinpyrazone) that increase the renal clearance of uric acid. When this treatment is begun, measures to assure a large volume of neutral or alkaline urine are essential. Alkaline potassium salts may be used rather than sodium bicarbonate when it is desirable not to give excess sodium. The thiazides may increase the concentration of uric acid in the blood by lowering its tubular secretion, and thus precipitate clinical gout and uric acid calculi. Potassium depletion *per se* may reduce the renal clearance of uric acid; therefore, a deficiency of this ion must be avoided when thiazides are given.

Any disorder causing hypercalcemia may be complicated by impairment of kidney function, ranging from a minimal defect in concentrating capacity to progressive renal failure. Deposition of calcium salts occurs mainly in the vessels, tubules and interstitial tissue of the renal medulla. In the earlier stages of impairment, degenerative and necrotic alterations are apparent in the epithelium of the ascending loop of Henle, in the distal convoluted tubule and throughout the collecting system. Vascular disease and superimposed infection may play important contributory roles in the renal dysfunction associated with hypercalcemic nephropathy. One of the earliest signs is a diminished ability to concentrate the urine. Polyuria and polydipsia are often chief complaints. Rapid improvement in concentrating capacity frequently follows successful treatment of hypercalcemia. Proteinuria in hypercalcemic nephropathy is usually mild (less than 1.5 gm in 24 hours). The urinary sediment may be remarkably free of formed elements. Radiological evidence of stones or calcification of the kidney may be absent despite intensive nephrocalcinosis.

Treatment is aimed at the underlying cause of the hypercalcemia, but the degree to which impairment of renal function can be reversed is related to the extent of the scar formation, permanent medullary obstruction and infection, and to the presence of vascular disease. Even after hypercalcemia is relieved, renal function may remain depressed or deteriorate slowly, and occasionally it may improve. While hypercalciuria may be associated with nephrolithiasis, the hypercalcemia is the cause of the progressive nephrocalcinosis and renal failure.

In severe hereditary cystinuria a physiological disturbance causes the rate of cystine clearance to approach that of inulin. Cystine, which is poorly soluble in acidic urine, precipitates to form stones, and obstructive nephropathy may follow. Cystine also may form an insoluble complex with calcium. Treatment of this condition involves alkalinization of the urine, large fluid intake, and low protein diets.

It has been suggested that certain physiological substances (pyrophosphates and phosphorus pentoxide compounds) capable of forming soluble complexes with calcium are present in lesser quantities in persons with stones than in those with normal urine. However, it is not possible at present to estimate the importance of these deficiencies and other factors favoring the solubility or insolubility of stone precursors.

It is now evident that chronic potassium depletion can alter seriously both the function and structure of the kidney.[2] Potassium depletion may result from excessive loss of fluid from the gastrointestinal tract (as from laxatives and enemas),

excessive use of diuretics, aldosterone-producing tumors, Cushing's syndrome and renal disorders such as tubular acidosis and Fanconi's syndrome.

Potassium is the principal intracellular cation and it has a vital role in maintenance of the normal cell. However, little can be said about the manner in which potassium deficiency causes widespread alterations in cell function and in the structure of the nephron. Nephropathy can be suspected in a person with a history of prolonged potassium depletion, evidence of a low serum potassium level (usually less than 3.0 mEq per liter), polyuria, polydipsia, inability to form acidic urine, and minimal azotemia. Unfortunately, there is no pathognomonic histological lesion observable in the kidney. There is little published information regarding the reversibility of potassium-depletion nephropathy in man. In some patients, however, serial renal biopsy studies have shown complete repair several months after potassium repletion.

Vitamin D deficiency can result in a nonspecific proximal tubular hypofunction and aminoaciduria. Therapy consists of administering large doses of vitamin D, and complete recovery of tubular function usually occurs after about one month of treatment.

Disorders of the liver may be associated with renal abnormalities. Liver damage induced experimentally by choline deficiency may be associated with severe degenerative and hemorrhagic changes in the kidney. Hemorrhage, potassium depletion, hypotensive drugs and sedatives may contribute to the progressive reduction in renal blood flow and glomerular filtration rate, and to the resultant azotemia, which may occur with hepatic failure; however, the basic cause of the renal damage is unknown. The appearance of renal damage in association with liver failure has an ominous prognosis. There is no known specific therapy.

Diabetes mellitus has occurred after prolonged use of thiazide diuretics and commonly after use of diazoxide, a nondiuretic thiazide. The diabetes in such cases appears to be clinically identical to familial diabetes. However, there is not yet sufficient experience nor has enough time passed to evaluate the effect of this drug-induced diabetes on the kidney. There is no reason to believe the kidneys will be spared. The thiazides have also been associated with hyperuricemia. In fact, it appears that most, if not all, drugs which are organic acids will hinder the renal clearance of uric acid. This drug-induced hyperuricemia has been associated with clinical gout but the effect on renal tissue has not been reported. With more time and careful observations, it is very likely that renal damage characteristic of gouty nephropathy will be found. Although many drugs can raise the serum uric acid, the thiazides are most commonly implicated because they are used for long periods and the doses required to cause this adverse effect are relatively low.

Hypercalcemia is an uncommon adverse reaction to chronic usage of antacids. Although there is evidence that most, if not all, patients absorb some of the calcium carbonate antacid, only occasionally does significant hypercalcemia occur. It is likely that patients who have hypercalcemia from this cause absorb greater amounts of antacid or the antacid more efficiently complexes phosphate in the gut and thus promotes calcium absorption. When beginning patients on antacid therapy, it is wise to obtain a serum calcium determination about one week later. There is no doubt that significant renal disease can result from this drug-induced hypercalcemia.

It seems safe to conclude that other types of "toxic" nephropathy due to deficiency states or metabolic disorders will be revealed as understanding of the basic biochemical changes in disease increases.

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